or mucus. These are useful signs of possible colitis that should dictate other studies, or at least stopping the inducing antibiotic regimen.

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How Much Toxicity Is Necessary?

SINCE THE FORMAL recognition of the specialty of medical oncology, and the provision of resources through the legislation of the National Cancer Act in 1971, considerable progress has been made in the management of neoplastic disease in the United States. Now almost 50% of patients with serious forms of cancer survive for five years, and many are regarded as cured. For patients younger than 45 years of age there has been a definite reduction in cancer mortality rates. To a large extent, this can be ascribed to the development of effective forms of cancer chemotherapy. The notable advances in the management of diseases such as acute lymphocytic leukemia, Hodgkin's disease and testicular cancer have, however, come at some cost, in particular in the form of clinical toxicity of the treatment used. In general, antineoplastic agents have a relatively low therapeutic index, exerting their cytotoxic action through a direct attack on either DNA or its synthesis. Their ability to discriminate efficiently between normal and target tissues is somewhat limited. As a consequence, a wide spectrum of adverse reactions is expected and has become generally accepted by the profession and the public as an unfortunate but necessary concomitant of treatment. The problem is further compounded by the fact that modern anticancer treatment rarely involves the use of a single cytotoxic agent; more commonly, cancer is treated with a combination of drugs—with overlapping toxicity for a single organ system—or with a combined modality approach in which anticancer drugs are given along with radiation therapy.

In this issue of the journal, McDonald and Tirumali present a comprehensive review of the many forms of toxic reaction of the gastrointestinal tract that are potentially associated with treatment with antineoplastic agents. This list of adverse reactions is impressive but must be placed in some context in regard to actual incidence. A serious or even clinically detectable hepatotoxic reaction, as an example, is unusual and rarely limits treatment. In addition, there is a considerable and largely unexplained variation in the degree of toxic effects experienced by patients treated with an identical regimen, with some patients having no effect while others are devastated. For the more subjective reactions, the frequency and magnitude of response may be influenced by a patient's preconceptions regarding chemotherapy, as well as the extent of preparation they have received and rapport they have established with the treating physician. Nevertheless, the more common toxic effects—anorexia, nausea and vomiting—can have serious consequences on the effectiveness of overall management. The reaction may be so severe as to limit a patient's acceptance of further, and possibly curative, treatment. Equally important, there can be a deleterious effect on patient nutrition, which compounds the all-too-frequent state of malnutrition that accompanies advanced cancer and the associated cachexia syndrome.

During the past seven years our understanding of the importance of toxic reactions of the gastrointestinal tract has become more focused and enlightened. This has resulted in the development of more effective antiemetic agents such as tetrahydrocannabinol and metoclopramide hydrochloride, as well as the establishment of nutritional supportive care as an essential component of overall management. In many cases a physician has a relatively broad range of chemotherapeutic options to select from; within limits, toxicity can be purposely reduced through the appropriate choice of drugs, dosage and schedule. This also assumes that a physician has accounted for the large number of additional variables that have been recognized to influence the risk of toxic effects, such as a patient's age, nutritional status and extent of prior therapy, and the clinical pharmacology of the drugs to be used. The medical and ethical difficulties encountered in patient selection and in determining a safe and effective dose for an individual case cannot be underestimated.

A critical question, and one fraught with considerable controversy, is what degree of toxic effects, if any, is required to insure that an optimal therapeutic dose has been administered. Under unusual circumstances, best exemplified by the current treatment of acute myelogenous leukemia, profound if not life-threatening hematologic and gastrointestinal toxic reactions are unavoidable. For most solid tumors, however, I strongly believe that serious adverse gastrointestinal reactions are not only unnecessary, but possibly avoidable. For example, many women who receive full-dose adjuvant chemotherapy following a mastectomy experience a stimulated appetite and have impressive weight gain during the 6 to 12 months of treatment. Studies using animals and clinical experience have shown that the current armamentarium of anticancer drugs has a definite but limited capability to select out and destroy cancer cells. This process is strongly influenced by complex mechanisms of neoplastic cell resistance and normal tissue tolerance. To simply increase drug dosage has rarely been shown to result in a measurable positive

increment of tumor response, relative to what is achieved with the accepted "conventional" dose range. Rather, such an exercise has been consistently associated with greater toxicity, with a possible negative impact on patient survival. This therapeutic philosophy is not universally shared by all respected oncologists, particularly those schooled in an earlier era when a serious toxic reaction was regarded as the only endpoint for determining that a biologically active dose had been administered. The concept of high-dose treatment is still being actively explored in studies using autologous bone marrow stem cell rescue, and I await the results of these trials before revising my thinking on this matter.

The degree of selectivity that can be achieved should not be underestimated. The gastrointestinal mucosa, like the bone marrow, is in a constant state of cell renewal. On this basis, and from data derived from animal toxicology, crypt cells have been regarded as highly vulnerable to chemotherapeutic attack. The human small intestine is in actuality remarkably resistant. In the study of Smith and co-workers described in the review, they examined the effect on the small intestine of combination chemotherapy, of the type that is commonly used in the treatment of Hodgkin's disease, breast cancer and gastric cancer.[1] There was no influence on the absorptive function of the small bowel, as measured by standard clinical criteria, and mucosal morphology remained intact aside from a transient reduction in mitotic figures. Obviously, this reserve capability can be overridden if one purposely chooses to use extraordinary doses.

During the past decade we have witnessed encouraging and in some cases dramatic improvements in the life expectancy of selected groups of cancer patients. These have largely come as a direct result of the development of effective forms of antineoplastic chemotherapy. There is a basis for anticipating that conceptual and technologic advances in the fields of oncogene research and immunology will result in less empirical and more selective forms of cancer treatment in the future. Nevertheless, it is safe to say that the current established forms of treatment and their associated gastrointestinal toxic effects will continue to dominate during the next five years. One of the major challenges in the field of oncology during the 1980s is to not only improve the therapeutic efficacy of existing anticancer treatment, but to prospectively design and evaluate drugs, biologics and regimens that focus on the critical issue of quality of life.

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